The Effect of Atorvastatin on lung function and sputum cell count in Chronic Asthma patients

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Abstract
Background: Asthma is a chronic inflammatory disease with incomplete recovery. Atorvastatin has documented in vitro and vivo anti-inflammatory effect. So effect of atorvastatin in chronic asthma patient was studied in TB and chest department of Tertiary care hospital of central India.
Objective: The effect of Atorvastatin on lung function and sputum cell count in chronic Asthma.
Material and Methods: In randomized, parallel, double blind placebo controlled clinical trial 60 chronic asthma patients who were taking inhaled corticosteroids were to receive either Atorvastatin or placebo for 12 weeks. Pulmonary function test, sputum cell count & lipid profile were done.
Result: With Atorvastatin significant improvement in ACQ (asthma control questionnaire), significant decrease in SCC (sputum cell count) & significant reduction in risk of asthma exacerbations after 12 weeks. No significant improvements in all parameters were seen with placebo. It was observed that mean changes in ACQ, SCC were statistically significant p <0.05 in Atorvastatin group as compared to placebo group, but mean changes in FEV1 (pre) and FEV1 (post), PEFR were not statistically significant at 12 weeks between the 2 groups.
Conclusion: Atorvastatin significantly improved asthma control according to asthma control questionnaires & reduced risk of asthma exacerbations correlated with reduction in sputum cell count.
Key words: Chronic Asthma, Forced Expiratory Volume 1(FEV 1), Peak Expiratory flow rate (PEFR), Sputum cell count (SCC), Asthma control Questionnaire (ACQ).

1. Introduction
The asthma is one of the most common chronic diseases globally and currently affects ~300 million people. The prevalence of asthma has risen in affluent countries over the last 30 years but now appears to have stabilized, with ~10–12% of adults and 15% of children affected by the disease. The prevalence of atopy and other allergic diseases has also increased over the same time, suggesting that the reasons for the increase are likely to be systemic rather than confined to the lungs.1
Asthma is defined by the Global Initiative for Asthma (GINA) as:
“A chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.”2
β2 selective adrenergic drugs, inhalational & oral steroids,Mast cell stabiliser Cromolyn, Xanthine derivatives,
Leucotriene antagonists, are routinely used in the treatment of Asthma & monoclonal antibodies used in Resistant cases.3
Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase), which catalyses a rate limiting step in cholesterol synthesis.4 Statins have been advocated as antihyperlipidemic agents for years, however the cholesterol-independent also called “pleiotropic” effects of statins are being studied as a treatment for a variety of other conditions.5 Statins are now recognized as atypical anti-inflammatory agents possessing a variety of immunomodulating effects and have diverse anti-inflammatory effects in addition to their conventional lipid-lowering properties.3,5,6
A recent trial of atorvastatin in rheumatoid arthritis showed improvement in clinical outcome of this chronic disease.7 Atopic asthma is an immune mediated airway disease associated with eosinophilic airway inflammation and Th2 cytokine functional profile. Recent studies have shown that statin can effectively reduce these acute changes in murine
models of allergic lung inflammation. So it has been postulated that the anti-inflammatory effects of statins may have relevance for the treatment of asthma and other respiratory disease. Recent studies shown that they may be beneficial in chronic obstructive pulmonary disease (COPD), their use is associated with reduced decline in lung function, improved survival following COPD exacerbations and increased exercise capacity.

This study was planned to test that atorvastatin added to inhaled corticosteroid treatment improves lung function and sputum cell counts in adults patients with chronic asthma.

2. Material and methods

This was a Prospective, randomized, Parallel, double blind placebo controlled clinical trial in patients of chronic bronchial asthma. The trial was conducted as per the guidelines of the declaration of Helsinki & Tokyo. Ethical permission was obtained from institutional ethics committee of tertiary care government hospital of central India. Patient’s diagnosed cases of chronic bronchial asthma receiving inhalational corticosteroids and Salbutamol in the chest & TB department of the hospital, were included in the trial. The study was carried out from June 2012 to December 2012.

2.1 Aims and Objectives

This study was planned with the aims and objectives to study the effect of addition of atorvastatin to inhaled corticosteroid treatment on lung function and sputum cell counts in chronic asthma patients.

To measure the effect of atorvastatin on clinical parameters by: Spirometry – PEFR, FEV1; Sputum cell count; Asthma control questionnaire (ACQ); Asthma exacerbation rates.

The inclusion & exclusion criteria were:

2.2 Inclusion criteria

a. Diagnosed patient of chronic asthma: by spirometry and clinical examination. (With increase in FEV1 of > 12%, or 200 ml from baseline; Asthma control questionnaire score of ≥ 1 or Use of inhaled β2 -agonist on 5 or more days in the week.)

b. Age: 18-70 years.

c. Duration of asthma ≥ 1 year and on stable medication for 4 weeks.

d. Ready to give written informed consent.

2.3 Exclusion criteria

a. Pregnant & lactating women

b. Patients with unstable asthma

c. Patients on statin therapy for treatment of dyslipidemia.

d. Abnormal creatinine kinase and liver function tests plus myositis.

e. Patients taking drugs known to interact with statins

f. Any known sensitivity to statin, or previous evidence of myopathy

g. Abnormal serum creatinine levels.

Tablet Atorvastatin 40mg was purchased from a standard medical shop throughout the study. A matching Placebo was prepared from Lactose similar to Atorvastatin tablet. Salbutamol & Beclomethasone given by inhaled route by using Rotacap or meterdose inhaler. All screening investigations blood sugar- Fasting & postmeal, blood urea, serum creatinine, serum sodium & serum potassium, Liver function test SGOT, SGPT & Serum bilirubin & ECG was done & eligible candidates were included in the study. After clinical examination by physicians of Chest & TB department, spirometry-FEV1, PEF, FVC, Lipid profile-TG, VLDL, HDL, LDL & Total serum cholesterol, sputum cell count & asthma control questionnaire (ACQ) were done to get baseline data.

Total 60 patients were randomly divided in two groups A and B of 30 each, and were administered coded Atorvastatin 40mg daily or matching placebo of 12 weeks. The drug was issued to the patients for the duration of fortnight at a time. After completion of 6 weeks & 12 weeks study period, spirometry10 –FEV1, PEF, FVC, Asthma control questionnaire11 were repeated. After completion of 12 weeks- sputum cell count12, lipid profile was repeated. At the end of the study period the drug was decoded & results were calculated by paired t test & unpaired t test. Out of 69 patients randomised 60 patients completed the study. Seven patients were lost to follow up. Two patients were withdrawn due to adverse effects and exacerbation of Asthma from the trial.

1. Observation

The mean age of bronchial asthma patients was 42yrs. In Atorvastatin group 17 male (56.6%) & 13 females (43.3%). In placebo groups 12 males(40%) & 18 females(60%). There were 4 ex-smokers in Atorvastatin group & 3 in placebo group. Mean asthma duration in Atorvastatin group 24.1yrs & in placebo group 25.7yrs. Baseline use of reliever inhaler was similar in both group. Gr A-440mg Gr B-510mg.

There was no statistically significant difference between Atorvastatin (FEV1 pre 2.43 l/min, FEV1 post 2.70 l/min, PEF 287.03/min, ACQ 1.46 & SCC 10^6-155) & placebo group is (FEV1 pre: 2.44 l/min, FEV1 post 2.77l/min, PEF 291l/min, ACQ 1.49, SCC 1.41)
2. Results

Bronchial asthma was found to be equally seen in male and female patients. The effect of the study drugs after 6 & 12 weeks of administration on the spirometry findings is seen in Table 1, it was seen that there was a statistically significant change at 12 weeks in Atorvastatin group & placebo group compared to baseline FEV1 pre, FEV1 post, PEFR, ACQ, SCC. It was observed that mean changes in ACQ, SCC were statistically significant between 2 groups at 12 weeks, but the changes in FEV1 pre, FEV1 post, PEFR between the 2 groups were not statistically significant at 12 weeks.

It was observed that treatment with atorvastatin was associated with statistically significant reduction in the risk of exacerbation during study period which is similar finding with study in COPD patients.\(^3\)

Table 1: The effect of the study drugs after 6 & 12 weeks of administration on the spirometry findings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Atorvastatin Group (n=30)</th>
<th>Placebo Group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (pre) l/min</td>
<td>2.43 ± 0.10</td>
<td>2.44 ± 0.14</td>
</tr>
<tr>
<td>FEV1 (post) l/min</td>
<td>2.70 ± 0.10</td>
<td>2.77 ± 0.14</td>
</tr>
<tr>
<td>PEF l/min</td>
<td>287.03 ± 18.51</td>
<td>291.90 ± 14.01</td>
</tr>
<tr>
<td>ACQ</td>
<td>1.46 ± 0.13</td>
<td>1.49 ± 0.13</td>
</tr>
<tr>
<td>SCC (10⁶)</td>
<td>1.55 ± 0.11</td>
<td>1.41 ± 0.09</td>
</tr>
<tr>
<td>Male (%)</td>
<td>17(56.66)</td>
<td>12(40)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>13(43.33)</td>
<td>18(60)</td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>43.13 (10.61)</td>
<td>41.73 (11.41)</td>
</tr>
<tr>
<td>Asthma duration in years (SD)</td>
<td>24.1 (15.0)</td>
<td>25.7 (18.4)</td>
</tr>
<tr>
<td>Beclomethazone daily dose .mg (SD)</td>
<td>440 (309)</td>
<td>510 (249)</td>
</tr>
<tr>
<td>Puffs of reliever (salbutamol) used daily (SD)</td>
<td>2.1 (2.1)</td>
<td>2.5 (2.0)</td>
</tr>
</tbody>
</table>

Data represented as mean (SD)

Table 1: shows demographic characteristics of patients at baseline represented as mean (SD). Both the groups were comparable and there was no statistically significant difference between two groups at baseline. 13.33% in the atorvastatin and 10% in the placebo group were former smokers. The mean duration of asthma was 24.9 years. Baseline use of reliever inhalers was similar between groups. Total mean (SD) number of puffs of reliever inhaler was 2.3. There was no significant difference in No. women in both groups (43.33% vs. 60%); Shows FEV1 (pre), FEV1 (Post), PEF, ACQ and SCC in both groups at baseline given as mean ± SEM. There was no statistically significant difference between atorvastatin and placebo group in FEV1 (pre), FEV1 (Post), PEF, ACQ and SCC in Chronic asthma patients at baseline.

Table 2: Effect of drug in both groups on FEV1 (pre), FEV1 (Post), PEF, ACQ and SCC in Chronic asthma patients at 6 and 12 weeks.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Atorvastatin Group (n=30)</th>
<th>Placebo Group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1(pre) l/min</td>
<td>2.43 ± 0.10</td>
<td>2.51 ± 0.10</td>
</tr>
<tr>
<td>FEV1(post) l/min</td>
<td>2.70 ± 0.10</td>
<td>2.79 ± 0.11</td>
</tr>
<tr>
<td>PEF l/min</td>
<td>297.04 ± 18.56</td>
<td>295.43 ± 18.81</td>
</tr>
<tr>
<td>ACQ</td>
<td>1.46 ± 0.13</td>
<td>1.35 ± 0.13</td>
</tr>
<tr>
<td>SCC (10⁶)</td>
<td>1.55 ± 0.11</td>
<td>1.41 ± 0.09</td>
</tr>
</tbody>
</table>

Values are given as Mean ± S.E.M. P < 0.05 is indicated in the table by * sign. P < 0.1 is indicated in the table by ** sign. Shows FEV1 (pre), FEV1 (Post), PEF, ACQ and SCC, in atorvastatin and placebo group. It was observed that there was a statistically significant change at 6 weeks and 12 weeks in atorvastatin and placebo group compared to baseline (p<0.05). Sputum cell count was not done at 6 week.

Table No.3: Changes in Various Parameters from Baseline to 12 weeks in Atorvastatin group and Placebo group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change from Baseline at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atorvastatin (n=30)</td>
</tr>
<tr>
<td>FEV1 (pre) l/min</td>
<td>0.171 ± 0.081</td>
</tr>
<tr>
<td>FEV1 (post) l/min</td>
<td>0.215 ± 0.058</td>
</tr>
<tr>
<td>PEF l/min</td>
<td>31.28 ± 6.26</td>
</tr>
<tr>
<td>ACQ</td>
<td>-0.650 ± 0.13*</td>
</tr>
<tr>
<td>SCC (10⁶)</td>
<td>-0.414 ± 0.073 *</td>
</tr>
</tbody>
</table>

Values are given as Mean ± S.E.M. Table 3: Shows mean changes in various parameters from baseline to 12 weeks in Atorvastatin group and Placebo group. It was observed that mean changes in ACQ, SCC was statistically significant with P < 0.05. But FEV1 (pre), FEV1 (post), PEF, were not statistically significant at 12 weeks between the two groups.
3. Discussion

This is a randomised controlled study conducted to study the effects on asthma control and airway inflammation of oral atorvastatin in adults with chronic asthma. We observed that there was a significant improvement in clinical parameters of asthma like FEV1, PEFR at 12 weeks of treatment compared to baseline but there was no significant improvement in these clinical parameters when both atorvastatin and placebo group were compared with each other. Similar study with Simvastatin showed no significant reduction of inflammatory markers in COPD patients.

From baseline to 12 weeks, there was a significant improvement in the atorvastatin group compared to the placebo group in the ACQ score and reduction in total sputum cell count (SCC) i.e. indicator for inflammation. The lack of any improvement in FEV1 & PEF in our study of confirms and extends the finding of Hothersall et al (2008).

Braganza et al (2010) in their 8 week study found significant improvement in asthma control Questionnaire score (ACQ) and asthma-specific quality of life (AQLQ) with atorvastatin treatment, So improvement in ACQ & AQLQ is similar to our results.

Maneechotesuwan et al (2008) demonstrated that simvastatin enhances the anti-inflammatory effect of inhaled budesonide by suppressing eosinophilic airway inflammation in asthmatic patients by increasing production and release of IL10. Sputum eosinophil percentages were also reduced significantly by the combined therapy with budesonide and simvastatin compared with budesonide alone. An earlier trial in rheumatoid arthritis used atorvastatin with success. Kiener and colleagues showed that lipophilic statins such as atorvastatin and simvastatin have a much greater effect on inflammatory responses in human and animal models than the hydrophilic statin e.g. pravastatin etc. Atorvastatin was chosen as it has stronger inhibitor of the inflammatory response compared to simvastatin. Atorvastatin therapy had shown fall in C Reactive Protein levels within 4 weeks in patients of asthma. Atorvastatin on long term use had been shown to inhibit vascular and airway smooth muscle proliferation and lower the expression of the profibrogenic cytokine transforming growth factor (TGF)-β1.

Statins can influence the in vitro function of a range of inflammatory cells including T-lymphocytes, monocytes, macrophages, eosinophils and neutrophils.

In our study atorvastatin showed significant reduction in sputum cell count compared to placebo group. There are clinical studies clearly showed the effect of statin in reducing the eosinophilic and macrophage count in chronic asthma patients. Hothersall et al (2008) showed that there was significant decrease in sputum macrophage count and LTB4 concentration in statin group, Statin also reduces the sputum absolute alveolar macrophage count after atorvastatin treatment in asthma patients. Also statins possess potent antioxidative properties. Atorvastatin reduces the production of reactive oxygen species from bronchial epithelial cells and endothelial cells. Statins could affect the migration of inflammatory cells from blood into the airways & specifically interfere with cell binding and macrophage recruitment to the lung. This may contribute beneficial effect of statin in lung diseases. Statins has been shown to inhibit neutrophil chemotaxis by inhibiting human alveolar epithelial production of IL-8, which is an important cytokine involved in the recruitment of neutrophils.

Asthmas express the T_{h2} phenotype, whereas in normal airways subjects T_{h1} cells are predominantly expressed. T_{h1} cells, through the release of IL-5, are associated with eosinophilic inflammation and, through the release of IL-4 and IL-13, are associated with increased IgE formation. Much of the data from both laboratory and clinical trials suggest that statins causes preferential switch from T_{h1}-driven to T_{h2}-driven immune response. Atorvastatin in a murine model of multiple sclerosis induced preferential development of T_{h0} into T_{h2} cells, and suppressed production of T_{h1}-associated cytokines including TNFα, IFN-γ, and IL-2 decreasing inflammation.

So atorvastatin inhibit T-helper 1 differentiation and T-helper 2 polarization, with increased production of T-helper 2 cytokines (IL-4, IL-5, and IL-10) that promote activation and chemotaxis of eosinophils, switching inflammation from the T-helper 1 phenotype to the T-helper 2 phenotype. So above studies conclude that statin mainly useful for T_{h1} mediated diseases because of its preferential shift from T_{h1} to T_{h2}, not for predominantly T_{h2} mediated diseases like asthma. This explains the lack of statin response in asthma patient our study.

This lead to future area of investigation is to search for drugs like immunomodulators aimed at shifting CD4 lymphocytes from the T_{h1} 2 to the T_{h1} phenotype or at selective inhibition of the subset of T_{h2} lymphocytes directed against particular antigens.

References

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